DETAILED ACTION

STATUS OF THE APPLICATION

1. Receipt is acknowledged of Applicants' Amendments and Remarks, filed 20 December 2011, the matter of Application No. 10/58611. The Examiner further acknowledges the following:

Claims 1 has been amended.

INFORMATION DISCLOSURE STATEMENT

2. No new Information Disclosure Statement (IDS) has been submitted for review.

WITHDRAWN REJECTIONS

3. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

NEW REJECTIONS

In light of Applicants amendment to claim 1, the following rejections are new to address the amendment:

CLAIM REJECTIONS - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence

Claims 1-13 and 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al. (US 2002/0179096) in view of Kino et al. (US Patent 5, 871, 778).

Siegel et al. teaches a surgically implantable drug delivery system for long-term delivery of the antipsychotic drug – haloperidol (see Abstract); (page 2, paragraphs 0019-0021). The implantable delivery system contains a biodegradable polymer, preferably a lactide-glycolide copolymer (page 1, paragraph 0002); (page 3, paragraph 0023). Siegel et al. discloses an implant of polylactide-co-glycolide, one phase of which has slow release, the other having a faster release (paragraph 0024). The implant is specifically indicated for the treatment of psychotic disorders ((paragraph 0021) and (0032)). The implantable delivery system comprising the antipsychotic drug haloperidol provides superior treatment outcomes due to improved medication adherence. The implants are designed to last for months to years. Advantages of the implants include lower dosing, steady state serum drug levels and increased bioavailability (page 2, paragraph 0022). The implants can be removed and thus offers a degree of reversibility (page 1, paragraph 0010).

It is noted that Siegel does not teach their implant to be a "rod-shaped" structure. However, the particular shape of the implant would be based on personal preference and/or the particular intended use of the implant. Moreover, an effective shape can be determined by one of ordinary skill in the art in order to provide an optimal outcome. The particular shape of the implant being claimed does not render a patentable distinction over the disclosure of Siegel who clearly recognizes and teaches an implantable drug delivery system comprising an antipsychotic drug (haloperidol) in combination with biocompatible polymers, such as polylactic acid and polyglycolic acid, whereby the implant is removable and is effective for the treatment of psychotic disorders and conditions.

Thus, the instant invention would have been *prima facie* obvious to one of ordinary skill in the art, given the teachings of Siegel.

It would have been obvious to the skilled artisan at the time the invention was made to have administration of two formulations because it is routine in the art to administer drugs to the same patient in multiple different dosage forms in order to achieve a particular therapeutic effect. Furthermore, the implants taught in Sigel have a pattern of release characterized by an initial phase of slow release of haloperidol followed by a second phase of more rapid release (paragraph 0024). With regards to the new limitation that the time to maximum concentration of said drug in said subject ranges from about 20 days to about 190 days, Siegel teaches that the percent released of haloperidol is .33% during days 0-28 and .88%/day during days 28-140.

With regards to the limitations "whereby administering said first and second formulation results in therapeutic circulating levels of said drug, for a period of about 14-120 days, thereby being a method of treating a nervous system disorder", until some material difference(s) in the

properties of the composition are demonstrated, said limitation is considered by the Examiner to be directed towards the drug formulation which is instantly claimed. Furthermore, the limitation having circulating therapeutic levels of the drug is future intended use as a result of the composition being implanted and is given little patentable weight. Absent evidence to the contrary, it is expected that the formulation would achieve the same circulating levels as claimed.

Siegel teaches subcutaneous delivery (paragraph (0013)). Furthermore, Siegel teaches implantable drug delivery devices (abstract). These devices are fully capable of being implanted subcutaneously.

Siegel teaches that the implant comprises a PLGA (polylactic acid to polyglycolic acid) ratio of 75:25 (paragraph (0024)). Therefore, as per pending claim 9, the implants vary in terms of drug concentration, polymer composition, or combination thereof. Siegel also teaches the biodegradable polymer also comprises about 50 to 100% polylactide and 0 to 50% polyglycolide (paragraph (0023)). The range reads and falls within the range of said polymer 40-90%. The drug, haloperidol is disclosed to be in the preferred range of from about 20% to about 40% (paragraph (0023)). Also see Examples 4-5. This range reads on the range of therapeutic drug of 10-60%.

Siegel teaches that the therapeutic drug is present in an amount of 30%-60% of the mass of the implant (paragraph (0023)).

With regards to administration of the formulations, it would have been obvious to one of ordinary skill in the art to administer the formulation within 1-24 hours, cyclically, or within 160-200 days in order to achieve an additive synergistic effect of the drugs while prolonging the effect of the drug.

Siegel teaches the antipsychotic drug – haloperidol, used to treat psychotic disorders such as schizophrenia (paragraph 0032). Siegel discloses risperidone as a known antipsychotic drug (paragraphs (0009) and (0014)). While Siegel does not teach the antipsychotic drug – risperidone, for use in the invention, both of these drugs - haloperidol and risperidone are well-known effective psychotic medications useful for the treatment of psychotic disorders and would have equivalent efficacy, as evidenced by Kino.

Kino teaches a sustained release microsphere preparation produced by combining an antipsychotic drug such as haloperidol or risperidone with polymers such as polylactic acid, polyglycolic acid or the like (see column 2, line 45 - col. 3, line 16); Claims 5 and 8. The preparation of Kino aims to improve the maintenance therapy and increase patient compliance with hydrophobic antipsychotic drugs (col. 2, lines 15-29); (col. 2, lines 5-20). Additional antipsychotic drugs are disclosed at column 2, lines 45-55.

It would have been obvious to one of ordinary skill in the art in order to employ any antipsychotic drug, particularly risperidone, such as that taught by Kino, within the delivery systems of Siegel. One would do so with a reasonable expectation of success because Kino teaches preparations with the incorporation of antipsychotic drugs such as risperidone, haloperidol and the like which are known for their therapeutic efficacy of mental conditions (i.e., schizophrenia, bipolar disorder). The preparations enable improved patient compliance and effectively provide for the treatment and therapy of mental disorders and psychotic conditions. The expected result would be an improved drug delivery system comprised of antipsychotic agents for effectively combating psychotic disorders.

5. Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al. (US 2002/0179096) and Kino et al. (US Patent 5, 871, 778) as applied to claims 1-13, 15-20 above, and further in view of Sidman (US Patent 4, 352, 337).

Siegel does not disclose a rod shaped implant having a diameter of about 1 to 2mm, a length between about 10 and about 40 nm, or a combination thereof, however, Sidman teaches a rod-shaped implantable drug delivery device (col. 10 line 62-64 Fig 2). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate the implants as taught by Siegel into the shape of rods because it would have been obvious to one of skill in the art to form the implants in a shape that is desirable for ease of administration.

Sidman further teaches that the implant has a diameter between 2-4mm(col. 22 lines 45-40).

RESPONSE TO ARGUMENTS

6. Applicants' arguments have been considered but were not found persuasive. Applicants have submitted a declaration which has been considered but is not persuasive. Applicants' Declaration has also been considered but is not persuasive.

Applicants argue that nowhere does Sigel teach or suggest a biodegradable polymer that comprises a poly(lactide/glycolide) (PLGA) copolymer at a concentration of about 40-90% (w/w) and a drug that comprises risperidone, 9-OH-risperidone, or an active metabolite thereof at a concentration of about 10-60% w/w. Applicants argue that Sigel relates to haloperidol loaded implant, not risperidone loaded implant.

Applicants go on to argue that although Kino describes a laundry list of active materials including risperidone, it provides no data or support for how much of each active ingredient that can be loaded into each biodegradable polymer. Therefore, at the minimum, Kino provides a general guidance for producing only a microcapsule with no expectation of success with respect to specific amount of drug for each combination of the drug and the polymer for an implant. Applicants argue that it is well known in the art that concentrations are critical for making a polymer-based drug implant because of possible saturation and subsequent crystallization of the drug. Therefore it would be unreasonable to expect initial theoretical drug concentrations of 10% or more, without any data. In addition, a combination of a drug and a polymer may exhibit differing physiochemical properties at various concentrations, and thus one could not expect or predict whether the arrangement and/or conformation of molecules in the crystal lattice would change while combining the drug and the polymer during solvent casting or other approaches to form an implant. Therefore, an attempt to incorporate as much as 10-60% risperidone into PLA:PGA copolymer cannot be expected in view of Siegel, Kino, or any reference in the art. It would be unreasonable to expect initial theoretic drug concentrations of 10% or more due to possible saturation and subsequent crystallization of the drug.

In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007).

The Examiner respectfully submits in this case, the primary reference of Siegel teaches an implantable drug delivery system for long- term delivery of the antipsychotic hydrophobic drug haloperidol. Examiner agrees that Siegel does not teach an implant loaded with risperidone. Siegel does teach the claimed encapsulating polymer and the advantages to be obtained by its use. Examiner also agrees with applicant that Kino teaches many different drugs but also specifically teach the equivalence of haloperidol and risperidone in the same context as the instant invention. Kino teaches to use the disclosed drugs in conventional amounts and therefore do not disclose data or support for how much of each drug should be loaded into an insert for use in a patient because such dosages are well known to those of ordinary skill in the art.

It would have been obvious to one of ordinary skill in the art in order to employ risperidone within the delivery systems taught by Siegel for providing a new long-acting implant for the treatment of schizophrenia, bipolar disorder, and behavior problems in people with autism. One would do so, because Kino teaches that preparations comprising PLA:PGA matrix can successfully accommodate various hydrophobic antipsychotic drugs, e.g., risperidone, haloperidol and the like, which are known for their therapeutic efficacy of mental conditions.

The argument that "Kino describes a laundry list of active materials including risperidone but provides no data or support for how much of each active ingredient can be loaded into each biodegradable polymer" was not rendered persuasive. The fact that the reference recognizes use of risperidone for the treatment of mental conditions such as schizophrenia and bipolar disorder is ample to meet Applicant's claimed limitations. With respect to the amount of biodegradable polymer, note that the implant of Siegel comprises a polylactic acid to polyglycolic acid, PLA:PGA ratio of 75:25, 50:50 and 100:0 (Para. 0023-0024, 0026; Examples 1 and 5). This

range reads on, falls within and overlaps with the range of said polymer (polylactide) of 40-90% in instant Claim 1. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists (*In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934; Fed. Cir.1990).*

With respect to the amount of active ingredient that can be loaded into each biodegradable polymer matrix, the instantly claimed drug percentage/range (10-60%) is very close and overlaps (20-40%) claimed by Siegel (Para. 0023, 0024, 0026, 0038, 0039) and (25-35%) disclosed by Kino (Col. 6, Lns. 1-20, 55-65; Col. 7, Lns. 18-25) . The Examiner points out that differences in concentration will not support the patentability of subject matter encompassed by the prior art, unless there is evidence indicating such concentration is critical.

In the Declaration provided, Applicants point out that different drugs have different release rates in PLGA matrices and thus to infer from one drug the effects of another is misleading.

The Examiner respectfully submits that it is acknowledged that no two drugs would behave exactly the same. However, haloperidol and risperidone are very structurally similar and it would be within the purview of one of ordinary skill in the art to account for the different release characteristics. There are a multitude of factors the skilled artisan would consider in making a drug matrix. One of the variables would be the polymer content and amount of polymer. The prior art teaches the same range of the same polymer and the same amount of drug to be incorporated with the polymer. The skilled artisan would know to account for the fact the different drugs behave differently. Upon looking at haloperidol and risperidone, they are very structurally similar that the skilled artisan would know they wouldn't behave exactly the same

but there would be expected some similarities in their profiles. Applicants provided Exhibit 1 to demonstrate that different drugs behave differently in PLGA matrices, however, the drugs that were tested were not structurally similar. Haloperidol was compared to aspirin, ibuprofen, HCTZ, Thiothixene and corticosterone all of which have different structures. It is noted that there is no example comparing haloperidol to risperidone. Applicants have not provided any comparison data between the two drugs haloperidol and risperidone to demonstrate that these two drugs would behave differently.

Applicants claim that with PLGA polymer, the incorporation efficiency decreases with increasing drug concentration and a person skilled in the art would not expect or predict that risperidone at concentrations of 10% or more would be effective with the claimed PLGA polymer.

In response the Examiner respectfully submits that this argument is not found to be persuasive because the prior art teaches loading drugs at the claimed concentration ranges in PLGA polymers. Therefore, the fact that 10% or more of the drug could not be predicted to be effective with the claimed PLGA polymer is not found persuasive.

The Examiner emphasizes that Siegel and Kino disclose delivery system comprising PLA:PGA polymeric matrix and hydrophobic drug incorporated therein. It is a position of the Examiner that optimization of such a delivery system would involve variation of polymer molecular weight; polymer mixture composition; solvents; methods for incorporating a drug into the matrix and for solvent evaporation. With regard to the PLA:PGA matrix, this technique has been studied in considerable detail providing correlation between drug hydrophobicity and polymeric composition (J Biomater Sci Polym Ed. 1997;9(1):75-87; J Biomater Sci Polym Ed.

1997; 8(12):905-17; J Biomater Sci Polym Ed. 2000; 11(3):301-318; J Biomater Sci Polym Ed. 2001;12(1):21-34 as example). Further, Kino discloses the PLA:PGA microcapsules comprising risperidone prepared in dichloromethane, i.e., a good solvent for the drug (Col. 6, Lns. 1-20). Applicant utilized acetone (Para. 00210 and 00194), which is known to ease risperidone crystallization (U.S. 6,750,341). Altogether, it is a position of the Examiner that optimization of implant characteristics would be carried out by one skilled in the art via manipulative experimentation including solvent casting conditions, polymer composition and initial concentrations of drug.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to determine suitable ranges or percentages of hydrophobic drug via routine/manipulative experimentation, to obtain the best possible results, as these are variable parameters attainable within the art. Risperidone and haloperidol have very close structural similarity and it is expected that they would behave in a very similar fashion. Furthermore, no unexpected or superior results have been observed in the instant amounts or ranges claimed. The prior art clearly teaches a similar formulation having similar ingredients, used for the same field of endeavor, as that desired by Applicants. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Danah Al-awadi whose telephone number is (571) 270-7668. The examiner can normally be reached on 9:00 am - 6:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/DA/
Examiner, Art Unit 1615

/Robert A. Wax/
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